SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLES

Table S1: Final estimates of the baseline parameters

Glucose, insulin, GLP-1, glucagon and GIP estimated baseline values

Estimated baseline values	Description	Estimate	RSE (%)
glucose baseline values			
BSLglc (mM) Landersdorfer	glucose baseline Landersdorfer study	10.8	2.13
BSLglc (mM) Jauslin	glucose baseline Jauslin study	7.8	0.97
BSLglc (mM) Jauslin ID 4002	glucose baseline Jauslin study ID 4002	8.18	1.72
insulin baseline values			
BSLins (pM) Landersdorfer	insulin baseline Landersdorfer study	131	9.96
BSLins (pM) Jauslin	insulin baseline Jauslin study	52	6.5
BSLins (pM) Jauslin ID 4002	insulin baseline jauslin study ID 4002	75.1	6.68
GLP-1 baseline values			
BSLglp (pM) Edholm ID 6001	GLP-1 baseline Edholm study	15.6	3.48
glucagon baseline values			
BSLglg (pM) Edholm ID 6001	glucagon baseline Edholm study ID 6001	24.2	1.25
BSLglg (pM) Edholm ID 6004 and 6005	glucagon baseline Edholm study ID 6004 and 6005	28	1.47
BSLglg (pM) Larsen	glucagon baseline Larsen study	28.2	6.82

*RSE (%) is calculated as SE/Estimate*100*

Table S2: Final estimates of the meal specific parameters

Meal intake parameters

Meal specific parameters		**Estimate**	**RSE (%)**
Edholm study specific glucose dosing parameters			
factor for Fglc	factor for glucose bioavailability	0.0562	-
KAglc (h^{-1})	glucose absorption rate constant	18.3	-
factor for Fglc ID 604 and 605	factor for glucose bioavailability	0.104	-
ALAG1 Edholm ID 604 and 605	lagtime for glucose dosing	0.182	-
D6 ID 6002	duration GIP infusion	3	-
D6 ID 6003	duration GIP infusion	2.9	0.148
glucose bioavailability breakfast			
Fb Larsen	glucose bioavailability breakfast	0.892	14.4
Fb LEAD-3 study	glucose bioavailability breakfast	0.34	14.6
Fb LEAD-6 study	glucose bioavailability breakfast	0.196	17.6
Fglc Camastra	glucose bioavailability	0.782	11.3
Fglc Vilsboll ID 11001	glucose bioavailability	0.65	8.67
Fglc Vilsboll ID 11002	glucose bioavailability	0.479	7.66
Fb Schneck	glucose bioavailability breakfast	0.714	18.3
Fb Jauslin	glucose bioavailability breakfast	0.446	9.25
glucose bioavailability lunch			
Fl Larsen	glucose bioavailability lunch	0.682	20.5
Fl LEAD-3 study	glucose bioavailability lunch	0.341	20.2
Fl LEAD-6 study	glucose bioavailability lunch	0.212	24.6
Fl Schneck	glucose bioavailability lunch	0.205	36
Fl Jauslin	glucose bioavailability lunch	0.294	10
glucose bioavailability dinner			
Fd Larsen	glucose bioavailability dinner	0.678	17.4
Fd LEAD-3 study	glucose bioavailability dinner	0.431	16.4
Fd LEAD-6 study	glucose bioavailability dinner	0.213	18.9
Fd Schneck	glucose bioavailability dinner	0.193	15.6
Fd Jauslin	glucose bioavailability dinner	0.287	10.4
glucose bioavailability snack			
Fs Larsen	glucose bioavailability snack	0.38	21.8
Fs Jauslin	glucose bioavailability snack	0.353	30.8

*RSE (%) is calculated as SE/Estimate*100*

SUPPLEMENTARY FIGURES

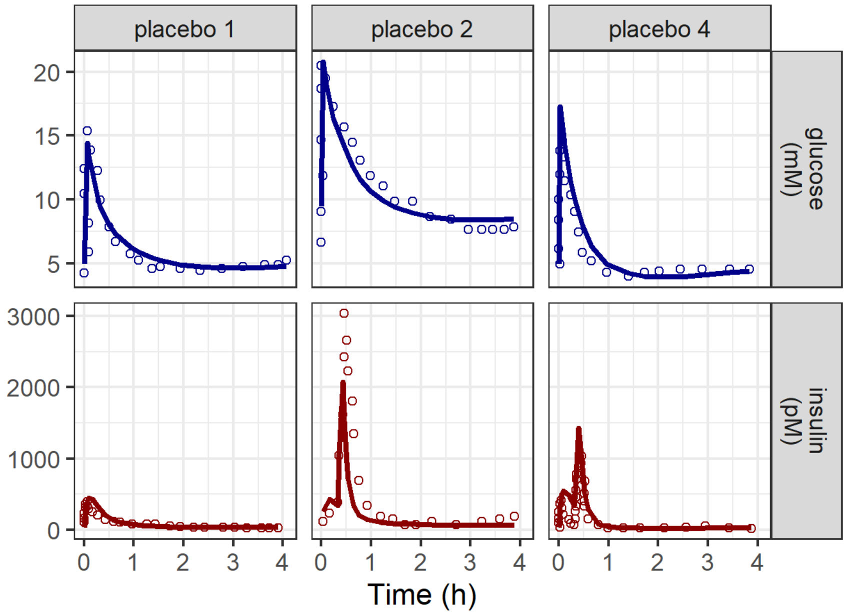

Figure S1: Model fit of the placebo arms from Silber et al. 2007 [12]

Dots represent the observations of the mean glucose and insulin concentrations following intravenous glucose provocations in healthy volunteers and type 2 diabetic patients. Lines represent the model prediction.

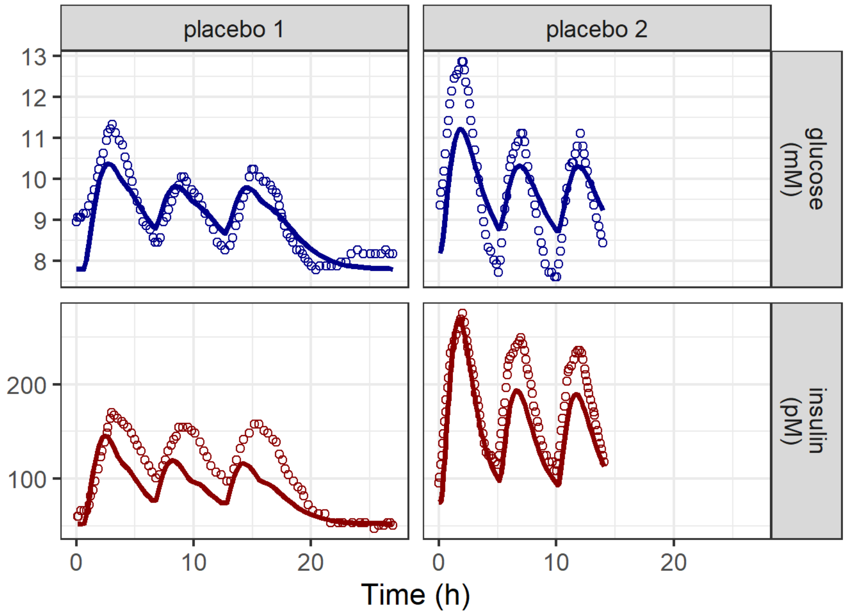

Figure S2: Model fit of the placebo arms from Jauslin et al. 2011[13]

Dots represent the observations from 24-hour glucose and insulin profiles following multiple meal tests were extracted from the data and added to the dataset. Lines represent model prediction.

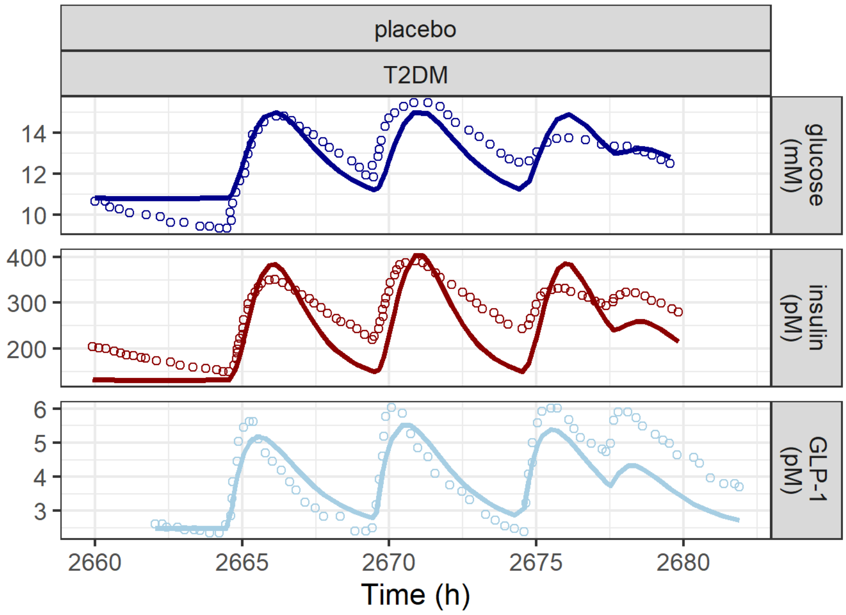

Figure S3: Model fit of the placebo arm from Landersdorfer et al. 2011 [14]

Dots represent the observations from median glucose, insulin and active GLP-1 data from the placebo group of the Landersdorfer study. Lines represent the model prediction.

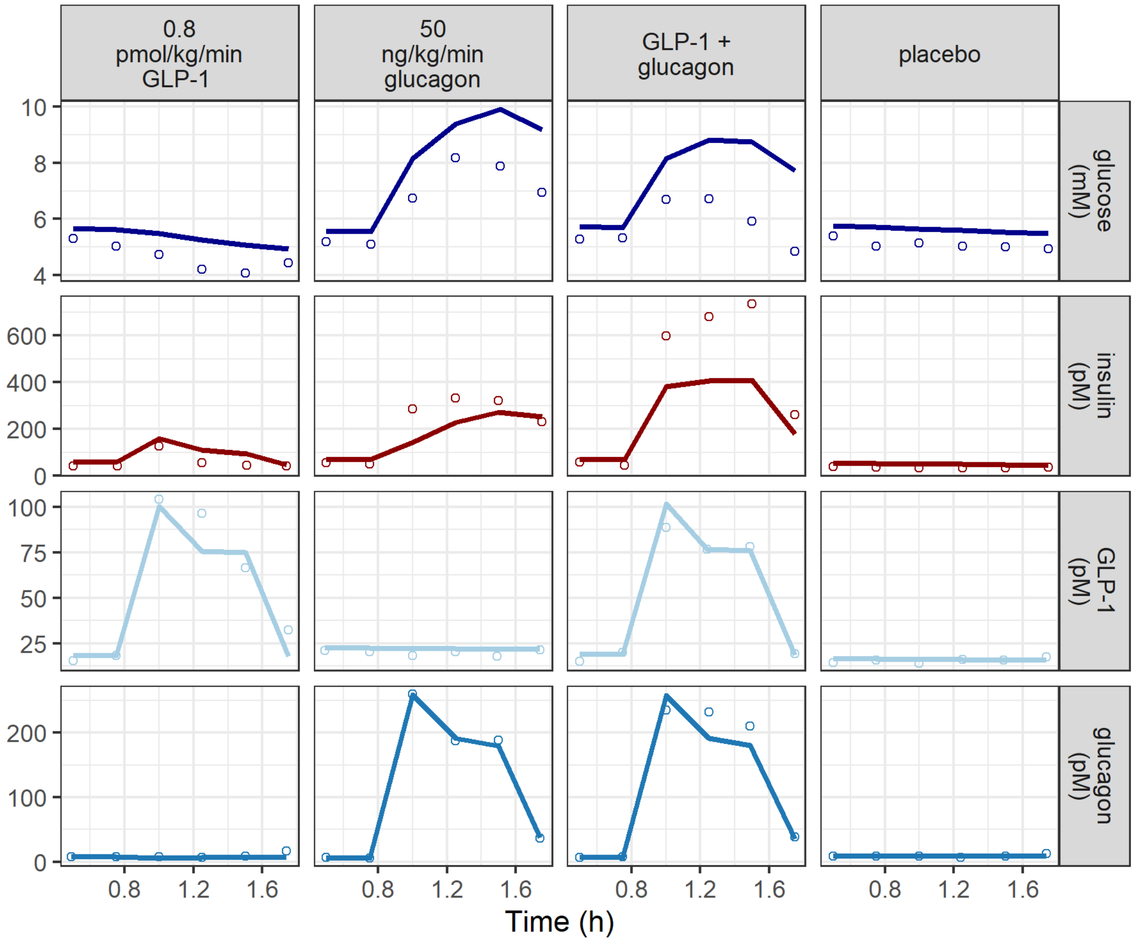

***Figure S4: Model fit of the placebo and treatment arms from Tan et al. 2012*[15]**

Dots represent the observations from mean glucose, insulin, total GLP-1 and glucagon profiles from a randomized, double blinded crossover study, where overweight or obese volunteers without diabetes received placebo infusion, GLP-1 alone, glucagon alone, or GLP-1 plus glucagon simultaneously. Lines represent the model prediction.

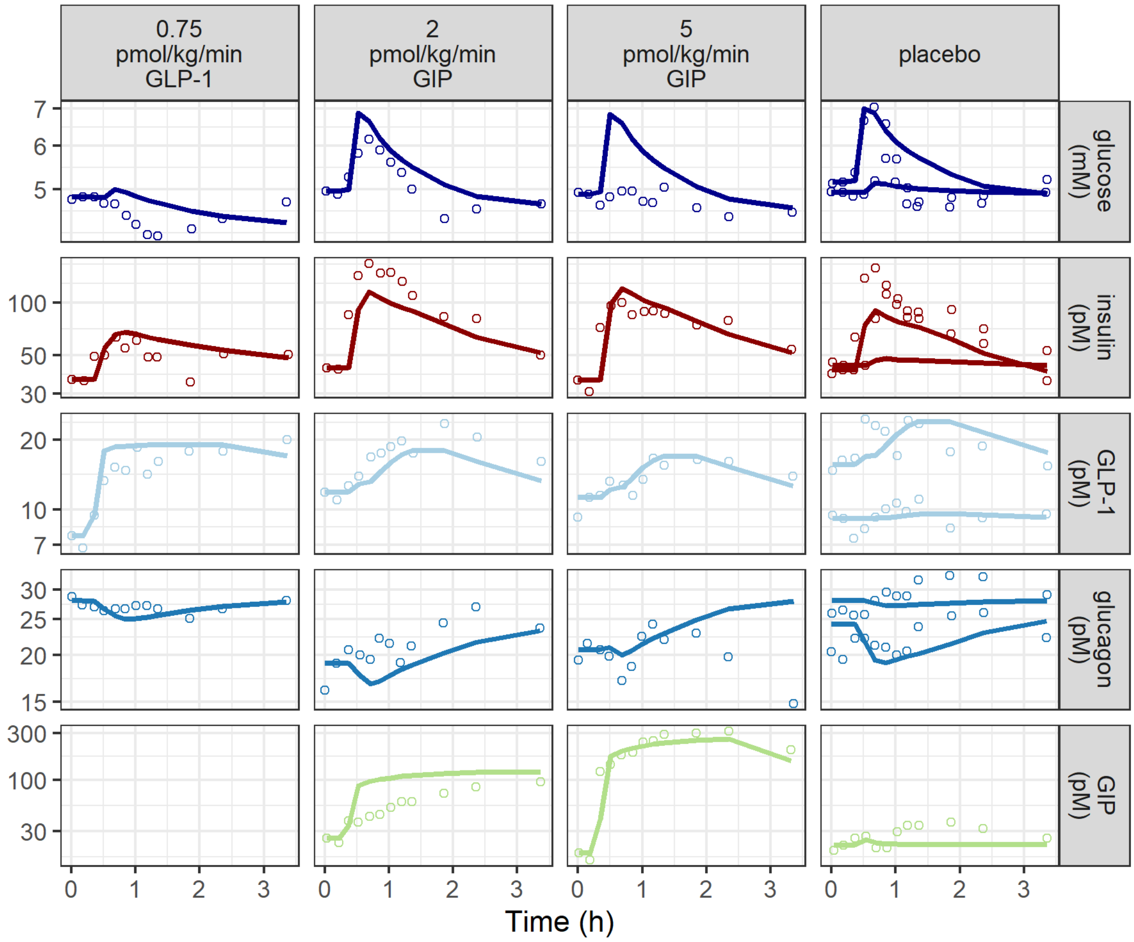

***Figure S5: Model fit of the placebo and treatment arms from Edholm et al. 2010*[16]**

Dots represent the observations from a randomized crossover single-blind study in healthy volunteers receiving GIP (2 or 5 pmol/ kg/min, GLP-1 (0.75 pmol/kg/min) or NaCl for 180 min with a radionuclide-labelled omelette and fruit punch (370 kcal). Multiple lines in the placebo figure represent the placebo groups from different treatment arms.

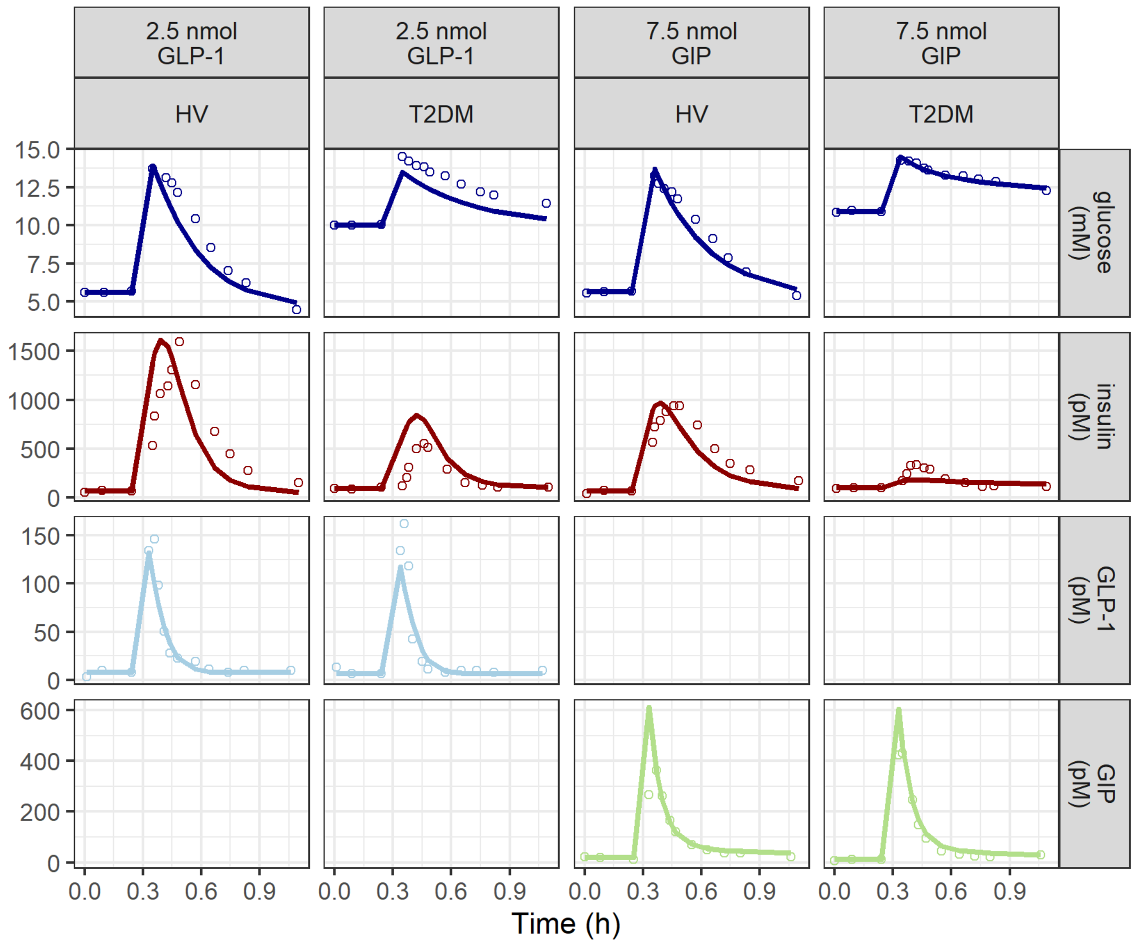

Figure S6: Model fit of the data from Vilsbøll et al. 2002[18] Protocol 1

Dots represent the observations from the Vilsbøll 2002 paper protocol 1 where T2DM patients and matched healthy subjects received intravenous bolus injections of GLP-1 (2.5 nmol) or GIP (7.5 nmol) concomitant with an increase of plasma glucose to 15 mmol/L. Lines represent the model prediction.

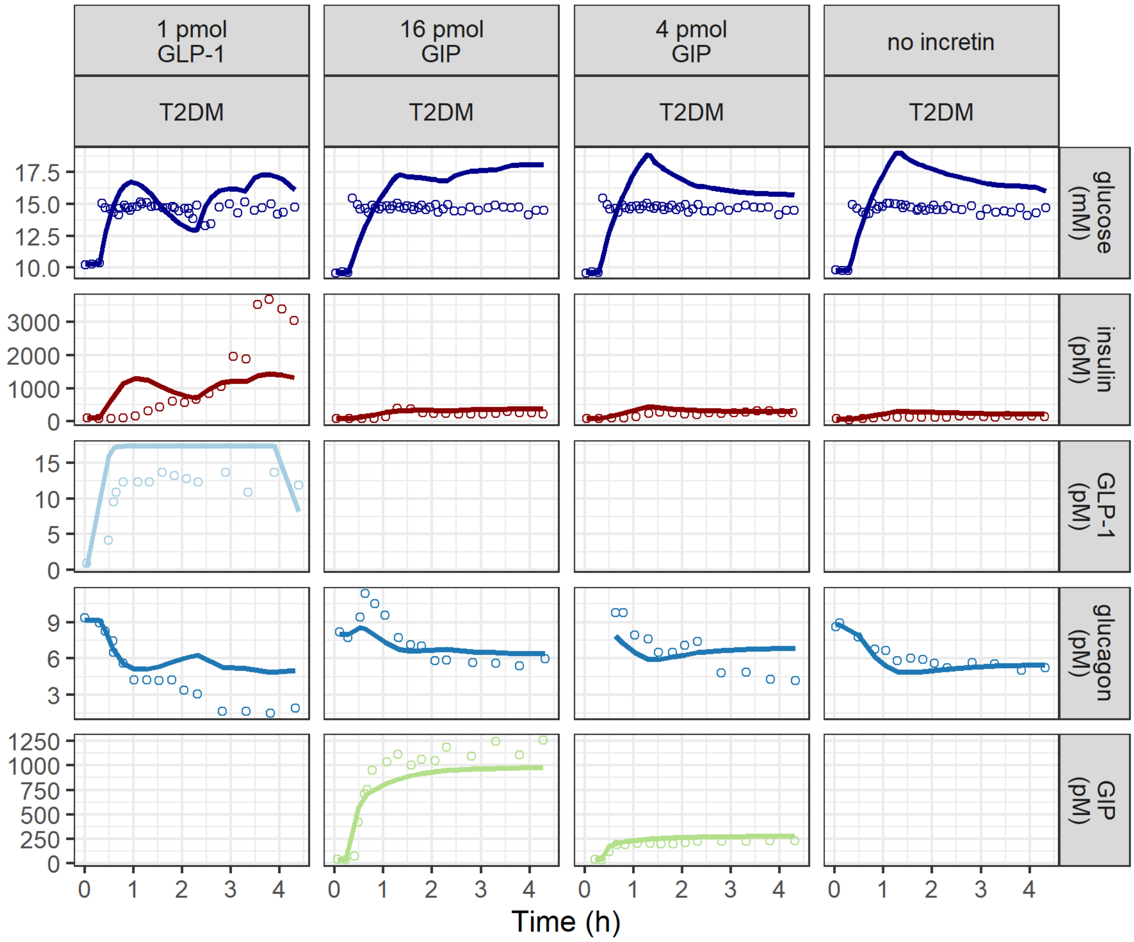

Figure S7: Model fit of the data from Vilsbøll et al. 2002[18] Protocol 2

Dots represent the observations from the Vilsbøll 2002 paper protocol 2 where T2DM patients underwent a hyperglycaemic clamp (15 mmol/L) with infusion (kg/min) of either: 1 pmol GLP-1, 4 pmol GIP, 16 pmol GIP or no incretin hormone. Lines represent the model fit.

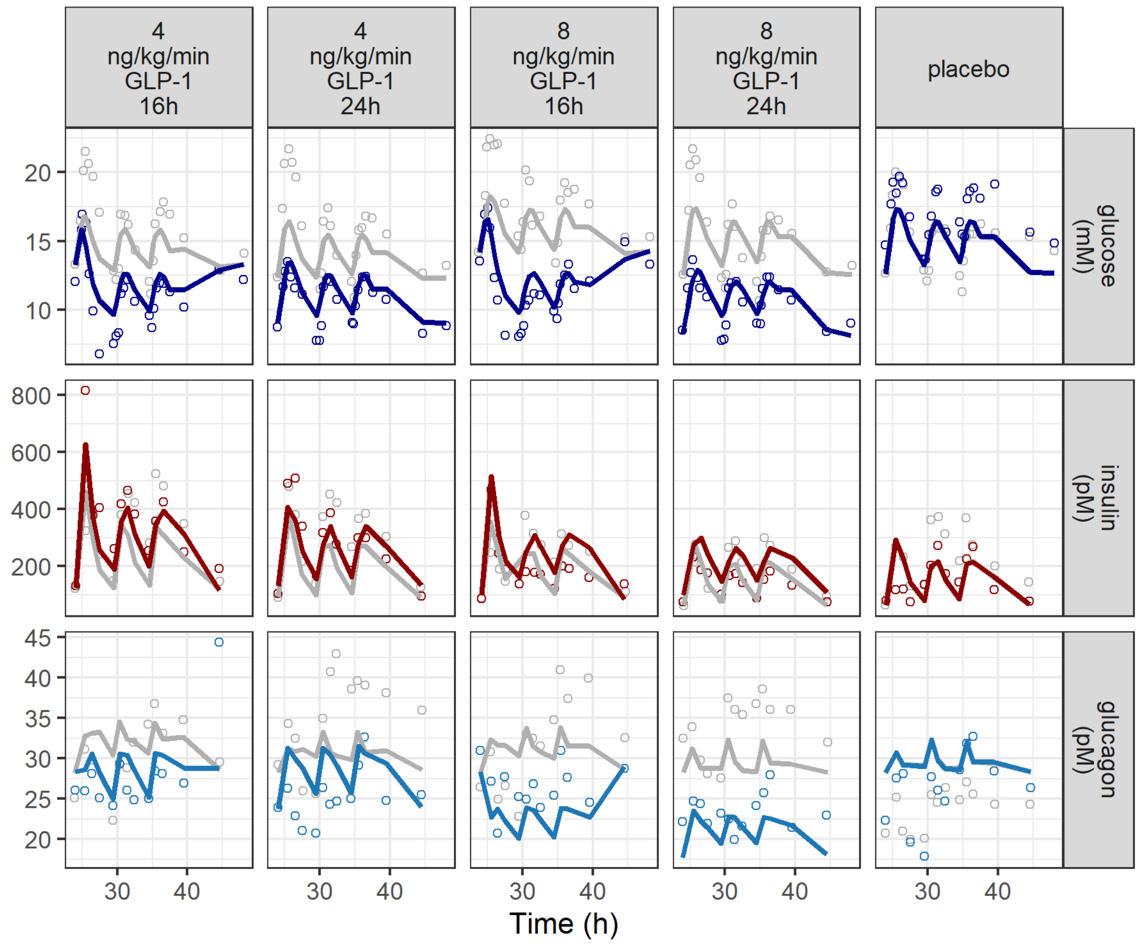

Figure S8: Model fit Larsen et al. 2001[19]

Coloured dots represent the day 7 observations of the 24h profiles from a single-centre, randomized, parallel, double-blinded, placebo-controlled trial in hospitalized patients who were randomized to receive infusions of either placebo or GLP-1 4 or 8 ng/kg/min for either 16 or 24 h per day for 7 days. The coloured lines represent the model fit. Grey dots and lines represent the pre-treatment observations and model prediction, respectively.

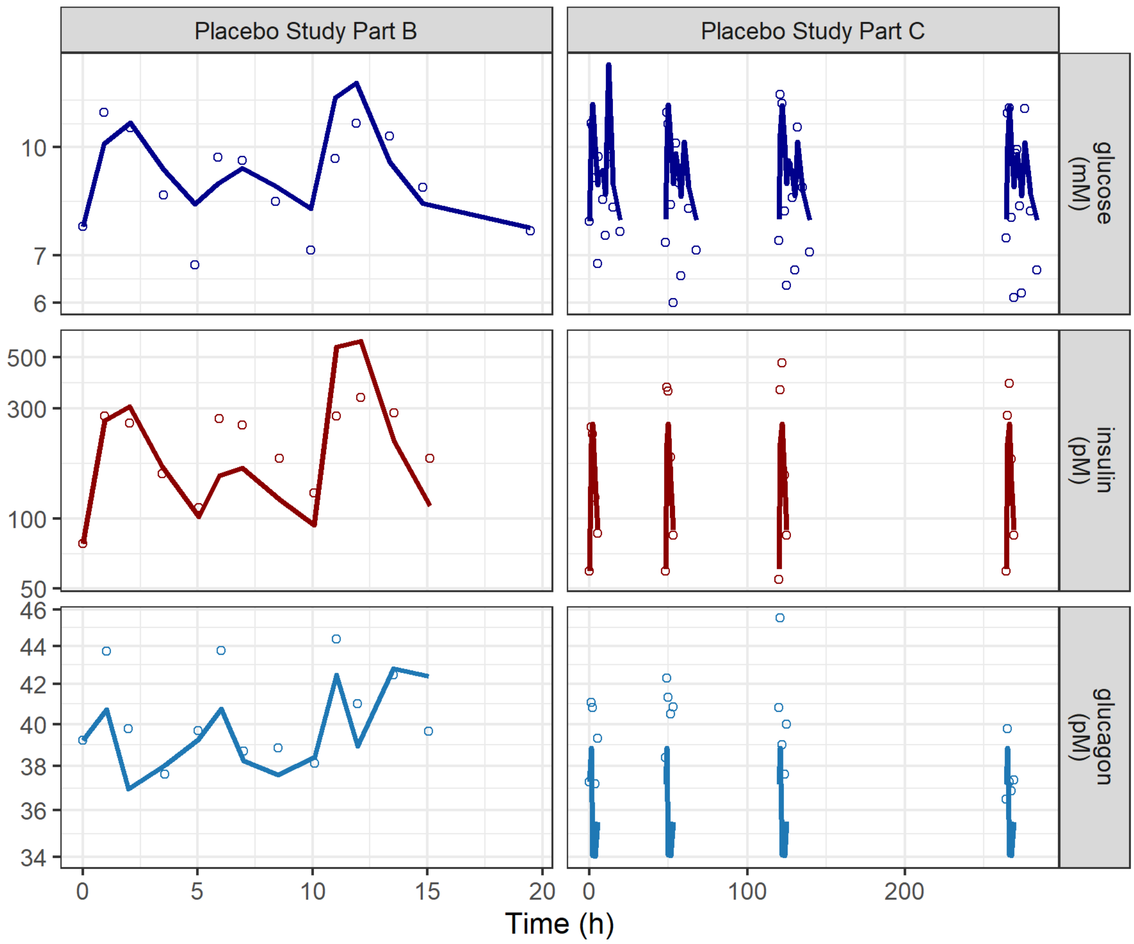

***Figure S9: Model fit of the placebo arms from Schneck et al. 2012*[20]**

Dots represent the observations from the placebo group profiles of a proof of concept study investigating the safety and tolerability of a novel oral glucokinase activator, LY2599506. Lines represent the model prediction.

Part B was a dose titration assessment in two temporally staggered cohorts of participants with T2DM. Subjects underwent titration of LY2599506 (n = 14) or placebo (n = 5) administered on a QID schedule for a total duration of 13 days. In Part C twice daily dosing of LY2599506 was compared to QID dosing in subjects with T2DM (n = 13) using a randomized two period crossover design. The duration of LY2599506 dosing in Part C was a total of 26 days (13 days for each treatment period).

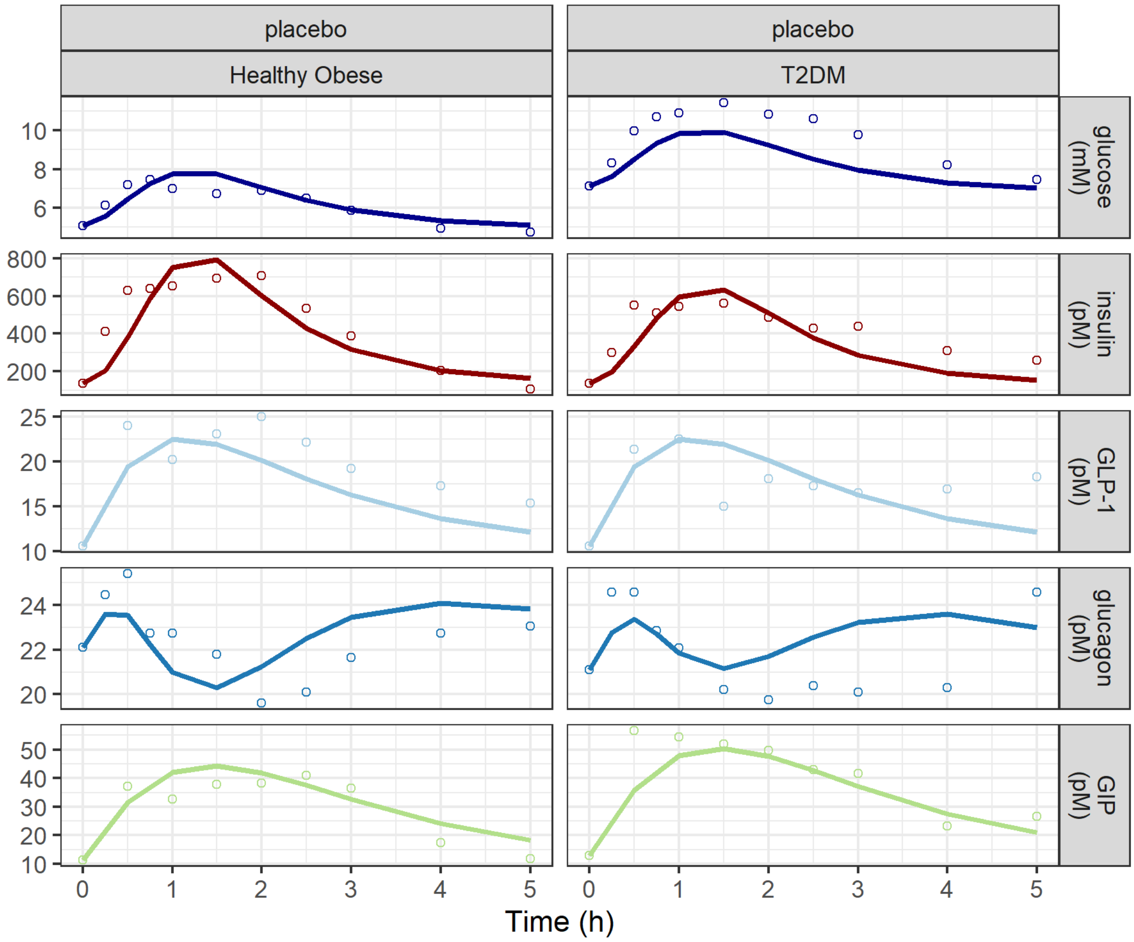

***Figure S10: Model fit of the placebo arms from Camastra et al. 2016*[21]**

Dots represent the observations during a meal test from a study including morbidly obese patients with T2DM and sex- and BMI-matched morbidly obese non-diabetic patients before bariatric surgery. Lines represent the model prediction.

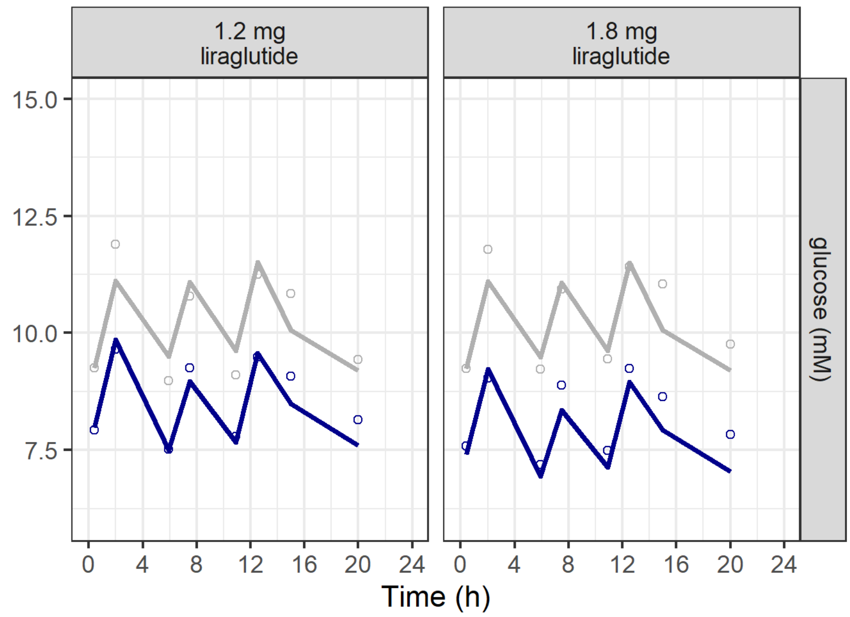

***Figure S11: Model fit of SMBG from the LEAD-3 study*[22]**

Dots represent the 24h self-measured blood glucose (SMBG) profiles from a double-blind, double-dummy, active-control, parallel-group study. In this study 746 patients with early T2DM were randomly assigned to once daily liraglutide, 1.2 mg or 1.8 mg, for 52 weeks. Lines represent the model prediction. Grey indicates the pre- and blue the end-of-treatment glucose profiles, respectively. Although liraglutide was administered once daily at any time of the day, it was assumed to be administered in the morning, half an hour before breakfast. Breakfast, lunch and evening meal times were assumed at 0.5, 6 and 11 h relative to liraglutide dosing, respectively.

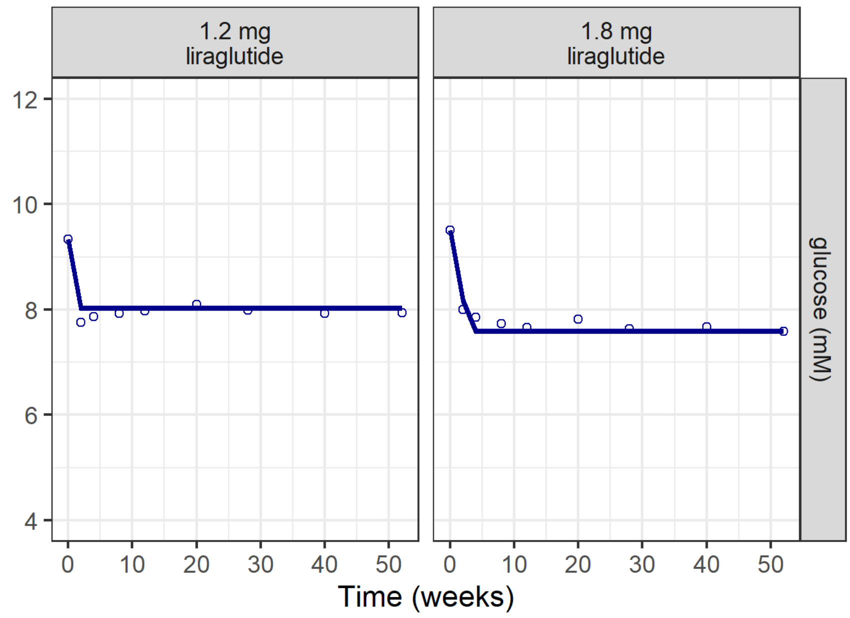

***Figure S12: Observed and predicted effect of liraglutide on FPG over time in the LEAD-3 study*[22]**

Dots represent the observed mean fasting plasma glucose (FPG) from a double-blind, double-dummy, active-control, parallel-group study, 746 patients with early T2DM were randomly assigned to once daily liraglutide, 1.2 mg or 1.8 mg, for 52 weeks. Lines represent the model fit.

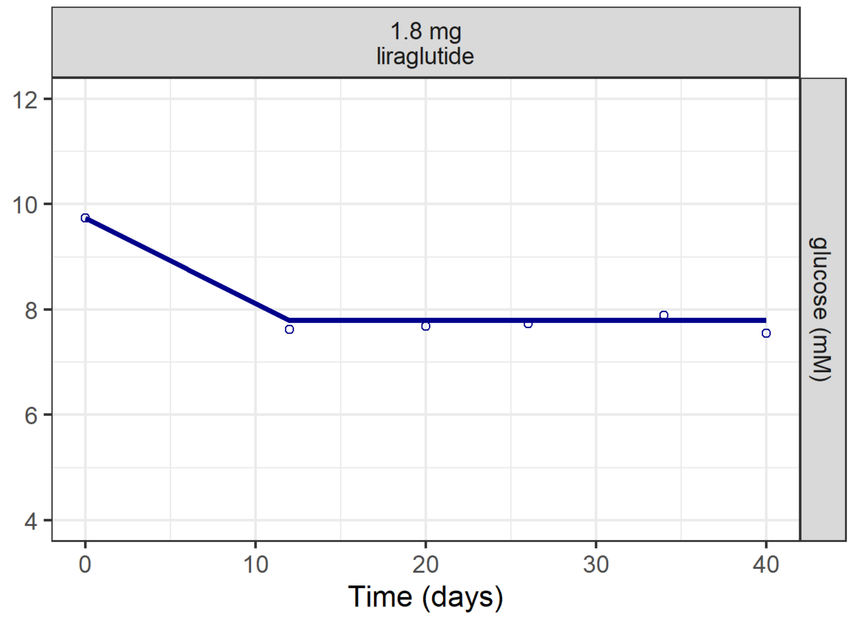

Figure S13: Observed and predicted effect of liraglutide on FPG over time in the LEAD-6 study[50]

Dots represent the mean observed FPG from the liraglutide arm from a study comparing liraglutide and exenatide in a 26-week study in T2DM patients. Line represents the model prediction.

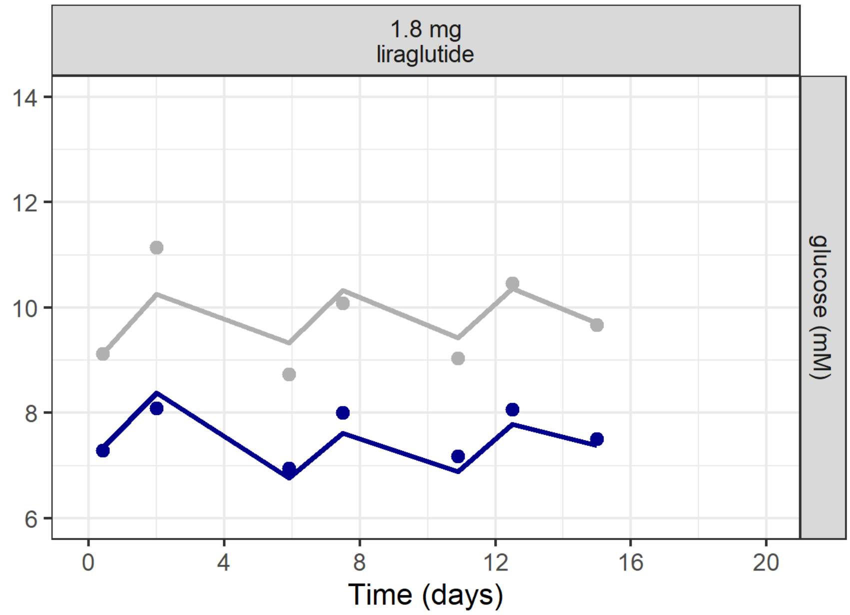

Figure S14: Observed and predicted effect of liraglutide on glucose over time in the AWARD-6 study[24]

Dots represent the 24h self-measured plasma glucose from the liraglutide arm of a phase 3, randomised, open-label, and parallel-group study at 62 sites in nine countries. Patients with inadequately controlled T2DM receiving metformin were randomly assigned to receive once-weekly dulaglutide (1.5 mg) or once-daily liraglutide (1.8 mg) for 26 weeks. Breakfast, lunch and evening meal times were assumed at 0.5, 6 and 11 h relative to liraglutide dosing, respectively. Lines represent the model prediction.

SUPPLEMENTAL BACKGROUND INFORMATION

S1 Model optimization

For model optimization, all available data (except for the dulaglutide data) were used to estimate the model parameters. All feedback mechanisms and biomarker disposition parameters that were not fixed to literature values were estimated simultaneously.

Nonlinear mixed effect modeling using NONMEM 7.3 with first-order conditional estimation method with interaction (FOCE+I) was used for data analysis and simulations[32]. Model selection was based on mechanistic plausibility of its parameter values, and drop in the objective function value. The objective function value is a goodness-of-fit measurement proportional to minus twice the log-likelihood.

All unknown parameters were estimated simultaneously. However, the glucose and insulin disposition parameters were fixed to the published values from the IGI model[12,13]. The GIP disposition parameters were estimated on the Vilsbøll publication[17] and kept fixed for the remaining of the model optimization. The EC_{50} value for the glucagon effect on glucose production was fixed to literature value[36]. Parameter correlations were used as an indication of potential model over-parametrizations. Where necessary, the model was simplified to account for high parameter correlations. Graphical assessment of model performance was carried out using standard goodness-of-fit plots, both for the entire dataset as well as by study and treatment arms.

For the external validation, a thousand sets of parameters were drawn from the covariance matrix to include parameter uncertainty in the simulation. The predicted time profiles (median and 90% CI) were overlayed with the observed time profiles.